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EXAMINER	
KIM, ALEXANDER D	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,662	RATCLIFFE ET AL.	
	Examiner	Art Unit	
	Alexander D. Kim	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-25 and 27-33* is/are pending in the application.

4a) Of the above claim(s) *7-25,27 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6 and 29-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/14/2005, 04/15/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Application Status

1. By virtue of a preliminary amendment filed on 04/15/2005, Claims 2 and 26 have been canceled; Claims 3-7, 16, 27 and 28 have been amended; and Claims 30-33 have been added. Thus, claims 1, 3-25 and 27-33 are pending in this instant case.

Election

2. Applicant's election with traverse of Group I, (Claims 1, 3-6, 29-33) in the reply filed on 05/21/2007 is acknowledged. The traversal is on the ground(s) that all the claims share a unity of invention because Groups I-III are united by the single inventive concept of identifying and using compounds that mimic or bind to FIH and the Examiner has not demonstrated that examining Groups I-III together would constitute a serious burden. This is not found persuasive because each Group represents a distinct independent invention and the search burden exists by the virtue of different class, subclass and distinct method steps between the Groups. Also, the search for each Group requires different key words because divergent subject matters on application. Searching altogether would create serious search burden on the examination. Furthermore, as previously noted, the technical feature of a method of identifying a chemical entity comprising comparing a structural model of FIH with a structural model of chemical entity is not special because it does not constitute an advance over the Hon et al. (2002, June 5th, Nature, vol. 417, page 975-978). Thus, the Groups I-III lack unity of invention.

Claims 7-25 and 27-28 are withdrawn from consideration as non-elected inventions. Claims 1, 3-6 and 29-33 will be examined herein.

Priority

3. The instant application is a 371 filing of the International Application No. PCT/GB03/04492 filed on 10/16/2003. The Examiner notes that the requirements of national stage entry of the instant application had been completed (note assigned U.S. filing date) within 30 months of the earliest claimed priority date; the related international application includes both a search report and a preliminary examination report.

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to foreign patent applications 0224102.4 (filed on 10/16/2002, United Kingdom) and 0226598.1 (filed on 11/14/2002, United Kingdom) in English.

Information Disclosure Statement

4. Information disclosure statements (IDS) filed on 04/15/2005 and 07/14/2005 have been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

Compliance with Sequence Rules

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. ' 1.821(a)(1) and (a)(2). However, this application fails to fully comply with the

requirements of 37 C.F.R. 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

a) The Table 2 contains many polypeptides without appropriate SEQ ID NOs.

b) The structural coordinates in Table 3 (total of four coordinates) teach an amino acid sequence since a particular atom is assigned to a linear amino acid sequence in order. As such, the amino acid sequence disclosed within the atomic coordinates must comply with the sequence rules. Labeling using a SEQ ID NO. must be inserted into the brief description of the drawings or into the Figure directly.

c) The polypeptide in page 35, line 16, does not have appropriate SEQ ID NO.

d) The polypeptide in Figure 3 or 4, require appropriate SEQ ID NOs.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Appropriate correction is required.

Objections to the Specification

6. The specification is objected to because of the following informalities:

a) The specification is objected to because the title is not descriptive of the claims. A new title is required that is clearly indicative of the invention to which the claims are drawn (see M.P.E.P. § 606.01). The examiner suggests the following new title, for example:

---A method of identifying a chemical entity which is a hydroxylase modulator---

b) The specification is objected because it does not recite all SEQ ID NOs filed in the sequence listing. The specification is confusing without such disclosure because it is unclear why said SEQ ID NOs are included in the sequence listing. Appropriate clarification is required.

Claim Objections

7. Claims 1, 4-6, 29, 32 and 33 are objected to because of the following informalities:

a) Claim 29 recites "co-ordinates". It should be ---coordinates. Appropriate correction is required.

b) Claims 1, 4-6, 29, 32 and 33 recite "FIH" or "HIF". The use of abbreviations FIH and HIF should be spelled out on a first appearance in claims. Appropriate correction is required.

c) Claims 1, 4-6, 29, 32 and 33 recite "FIH". The use of abbreviations FIH is not consistent through out the Claims. The FIH is the hydroxylase according to the Claims 5 and 32. However, it is unclear if the FIH is used as a chemical entity or if the FIH is the hydroxylase. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 6 and 33 are rejected under of 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6 and 33 recite the limitation of positions "asparagine 803", which is a relative term. The position number used in the claim to describe specific amino acid residues of HIF is unclear without the point of reference, preferably identified by SEQ ID No. Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 3-6 and 29-33 are rejected under 35 U.S.C. 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to methods comprising comparing a structural model of FIH with a structural model of chemical entity, wherein said structural model of FIH is derived from structural factors or structural coordinates from X-ray diffraction of a crystal comprising FIH; or using structural coordinates and deducing the structural coordinates, wherein the structural coordinates is obtainable by X-ray diffraction of a crystal comprising FIH. proteins in a suitable conditions and a precipitant for forming a protein crystal.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent

said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (paraphrased from *Enzo Biochemical Inc. v. Gen-Probe Inc.* (CAFC (2002) 63 USPQ2d 1609).

University of Rochester v. G.D. Searle & Co. (69 USPQ2d 1886 (2004)) specifically points to the applicability of both *Lily* and *Enzo Biochemical* to methods of using products, wherein said products lack adequate written description. While in *University of Rochester v. G.D. Searle & Co.* the methods were held to lack written description because not a single example of the product used in the claimed methods was described, the same analysis applies wherein the product, used in the claimed methods, must have adequate written description as noted from *Enzo Biochemical* (see above).

Instant application describes four structural coordinates of 1H2K, 1H2L, 1H2M and 1H2N (see Table 3) for a method of identifying , screening, characterizing or designing a chemical entity which binds to human Factor Inhibiting Hypoxia Inducible Factor (FIH) identified as Q969Q7 (NCBI database). The recited FIH is not defined by the instant specification; thus, the instant FIH has been interpreted as any factor that inhibit any protein or enzymes belonging to the same family as the HIF, "i.e. utilizing dioxygen (a cosubstrate), 2-oxoglutarate (2OG) (a cosubstrate) and Fe(II) (a cofactor). "Such enzymes are exemplified by phytanoyl coenzyme A hydroxylase, procollagen

prolyl-r-hydroxylase, procollagen prolyl-3-hydroxylase, gamma-butyrobetaine hydroxylase, Alk B (a DNA repair enzyme) and other including predicted 2OG oxygenases identified on the basis of sequence analysis including a sub-family related to FIH (Hewitson et al. J BIOL CHEM 277 (29): 26351-26355, 2002)" accroding to the instant specification page 2, middle. Thus, instant FIH encompasses any protein, enzyme, or polypeptide that inhibits enzymes belonging to the same family as the HIF, including the PMI or CAS1 shown in the sequence alignment of Figure 2-A, page 26354, by the Hewitson et al. Therefore, the instant claims encompass a method comparing any structure model derived from said genus factor inhibiting HIF family protein (FIH) with any chemical entity model structure having no structure limitation, wherein said structures are derived or obtainable by X-ray crystallography of a crystal comprising said FIH. The claimed method of using a genus of FIH structure described above cannot be adequately described by the disclosure of species of the structure coordinates in the Table 3. The species of instant case does not correlate structure and function from species to genus which have unlimited structure. Furthermore, the instant claims encompasses method of using a coordinate from X-ray diffraction of any FIH protein crystal. Because our understanding of crystallization mechanisms are still incomplete and the factors of macromolecular structure that are involved in crystallization are poorly understood, a method of the crystallization of a genus FIH encompassed by the breadth of the claims is not adequately described by the method of crystallization disclosed in the specification and the prior art. In general, for a species of crystallization to be adequately structurally described, the following must be adequately

disclosed: a composition of the protein solution and a precipitant solution used in crystallization (exact concentrations, pH and volumes of all molecules used in the crystallization) must be described, including (1) the protein (preferably a SEQ ID NO of all included residues) (2) any ligand added (3) the precipitant solution). The species of crystallization noted in Example 2 of the instant specification have not adequately met this burden and the crystallization encompassed by the breadth of the claims is not described.

A singular chemical composition can crystallize differently based on the crystallization conditions, and the space group and unit cell dimensions of a crystal of any given chemical composition can only be determined by analyzing that crystal's X-ray diffraction (Giege *et al.* Crystallogenesis of Biological Macromolecules: Facts and Perspectives. Acta Cryst., (1994) D50: 339-350). Therefore, the suitable condition disclosed in the specification to crystallize 16-314 of SEQ ID No. 1 cannot sufficiently describe a suitable condition of instant genus Claims.

10. Claims 1, 3-6 and 29-33 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for a method comprises using the structural coordinates of 1H2K, 1H2L, 1H2M and 1H2N (see Table 3) for a method of identifying, screening, characterizing or designing a chemical entity which binds to human Factor Inhibiting Hypoxia Inducible Factor (FIH, SEQ ID NO: undisclosed) identified as Q969Q7 (NCBI database), does not reasonably provide enablement for a method comprises using any structural model of any protein, enzyme,

or polypeptide that inhibits enzymes belonging to the same family as the HIF including a X-ray diffraction measurements of a genus crystal comprising said FIH related protein.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The breadth of the claims: A method of Claims 1, 3-25 and 29-33 are so broad as to encompass using a structural coordinates of any structure model derived from said genus factor inhibiting HIF family protein (FIH) with any chemical entity model structure having unlimited structure, wherein said structures are derived or obtainable (i.e. not a requirement) by X-ray crystallography, which requires any protein crystal comprising a genus FIH, wherein a FIH has been interpreted as any factor that inhibit any protein or enzymes belonging to the same family as the HIF, "i.e. utilizing dioxygen (a cosubstrate), 2-oxoglutarate (2OG) (a cosubstrate) and Fe(II) (a cofactor). "Such enzymes are exemplified by phytanoyl coenzyme A hydroxylase, procollagen prolyl-r-hydroxylase, procollagen prolyl-3-hydroxylase, gamma-butyrobetaine hydroxylase, Alk B (a DNA repair enzyme) and other including predicted 2OG oxygenases identified on the basis of sequence analysis including a sub-family related to FIH (Hewitson et al. J BIOL CHEM 277 (29): 26351-26355, 2002)" accroding to the instant specification page 2, middle. Also, the instant claimed method encompasses the use of any structure model derived from said genus factor inhibiting HIF family protein (FIH) with any chemical entity model structure having no structure limitation, wherein said structures are derived or obtainable (thus, not a requirement) by X-ray crystallography of any crystal comprising a FIH.

The nature of the invention: The invention is related to a method of using the structure coordinates of a human FIH (SEQ ID NO: undisclosed) identified as Q969Q7 (NCBI database) and a method comprising the x-ray crystallography for obtaining the structure coordinates of said human FIH. At the time of the invention, methods of

structure analysis using a three-dimensional coordinates and protein crystallization were well known in the art. However, claimed method of using any model or any variation of FIH structure derived from the coordinates of Table 3; and the ability to crystallize a given protein was, at the least, challenging to a skilled artisan as even minor alterations in the conditions of crystallization could result in altered crystal forms, crystals of sub-diffraction quality, or a lack of crystal growth (as described in further detail below).

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: The prior art by Hewitson et al. (2002) teach a method of using structures of model FIH family (i.e. CAS1 and PHD3, see Fig 2-B, page 26354), which can be used for instant claimed method of identifying, screening, characterising or designing a chemical entity that binds to FIH. Regarding a method of using any FIH crystals for X-ray diffraction measurements, the state of the art at the time of the invention acknowledges a high level of unpredictability for making the full scope of claimed crystals. For example, the reference of Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "crystallization is usually quite difficult to achieve" (p. 375) and that "well ordered crystals...are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Branden et al. further teaches that while there are instances where the structure of a protein has been resolved to a resolution of 1 Å, "only a few small proteins have been determined to such high resolution" (p. 382, first full paragraph). Also, Drenth et al.

("Principles of X-ray Crystallography", Springer, New York, 1995) teaches that "the science of protein crystallization is an underdeveloped area" and "protein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal as evidenced by Kierzek et al. (2001, *Biophys Chem* 91:1-20), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (p. 2, left column, top). Even minor alterations in the crystallization parameters can affect crystallization as evidenced by Branden et al., which teaches that the formation of protein crystals is critically dependent on a number of different parameters, including pH, temperature, protein concentration, the nature of the solvent and precipitant, as well as the presence of added ions and ligands to the protein (page 375, middle). Branden et al. teaches that even small changes in the crystallization parameters, *e.g.*, pH, can cause the molecules to pack in different ways to produce different crystal forms (page 374, bottom). Along these same lines, Wiencek (1999, *Ann Rev Biomed Eng* 1:505-534) teaches that "protein solubility will change dramatically as pH is altered by ~ 0.5 pH units...some systems are sensitive to pH changes as small as 0.1 pH units" (p. 514, bottom). In view of these teachings, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality protein crystals comprising any FIH can be achieved using the crystallization parameters in page 39 of instant specification known for human FIH identified as Q969Q7 (NCBI database). Alternatively, a skilled artisan would recognize

that it is highly unpredictable as to whether diffraction-quality crystals of any FIH protein can be achieved using any crystallization parameters.

The amount of direction provided by the inventor; The existence of working examples: The specification discloses many proteins which have similar amino acid sequences according to the Table 2, page 42, which belongs to cupin structural superfamily which includes instant genus FIH. The disclosure of four structure coordinates in Table 4 for the human FIH identified as Q969Q7 (NCBI database) do not provide guidance for one skilled in the art to practice the full scope of the claimed method for identifying a chemical entity for any FIH protein. Alternatively, the chemical entity identified by the stucture coordinates of Table 3 would not bind to all cupin structural superfamily. Furthermore, no single working example of chemical entity identified by four structure coordinates in Table 3 is disclosed by the instant application. Thus, the specification fails to provide guidance for a method of identifying any chemical entity which binds to a genus FIH and using any derived structure coordinates of model FIH from the coordinates of Table 3; and any crystallization conditions for crystallizing genus FIH proteins with an expectation of obtaining diffraction-quality crystals.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of protein crystallization were known at the time of the invention, these methods are specific to a particular protein with or without combinations of ligands as evidenced by the above teachings. Thus, a skilled artisan is left to experiment by a trial and error process to determine whether the disclosed crystallization conditions for the human FIH of Q969Q7 (NCBI database) can be applied

to crystallization of other proteins or whether any protein within the genus FIH under a different set of crystallization parameters.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make all methods and crystals as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one skilled in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or

in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. Claims 1, 3, 5-6 and 29, 31-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Hewitson et al. (May 31, 2002, The Journal of Biological Chemistry, vol. 149, page 26351-26355).

Claims 1, 3, 5-6 and 29, 31-33 are drawn to a method of identifying, screening, characterizing or designing a chemical entity which mimics or binds to FIH having method step of comparing a structural model of FIH with a structural model for said chemical entity, wherein said structural model of FIH is derived from structural factors or structural coordinates determined by subjecting a crystal comprising FIH to a X-ray diffraction measurements.

Because, the recited FIH is not defined by the instant specification, the instant FIH has been interpreted as any "Factor Inhibiting HIF molecule", not limited to, enzymes belonging to the same family as the HIF hydroxylases, i.e. utilizing dioxygen (a cosubstrate), 2-oxoglutarate (2OG) (a cosubstrate) and Fe(II) (a cofactor). "Such enzymes are exemplified by phytanoyl coenzyme A hydroxylase, procollagen prolyl-r-hydroxylase, procollagen prolyl-3-hydroxylase, gamma-butyrobetaine hydroxylase, Alk B (a DNA repair enzyme) and other including predicted 2OG oxygenases identified on the basis of sequence analysis including a sub-family related to FIH (Hewitson et al. J BIOL CHEM 277 (29): 26351-26355, 2002)" accroding to the instant specification page 2, middle. Thus, the PMI or CAS1 shown in the sequence alignment of Figure 2-A, page 26354, by the Hewitson et al. is encompassed by a very broad FIH.

Hewitson et al. teach a method comprising comparing a structural model of phosphomannose isomerase (PMI) complexed with zinc, which are encompassed by the term FIH and a chemical entity, respectively, as shown in the three-dimensional structure in Figure 2-B, wherein the PMI three-dimensional structure meets the recited limitation of "structural model of FIH derived from structural factors or coordinates determined by X-ray diffraction" in Claims 1 and 29. The binding of Zn in the protein crystal structure of Hewitson et al. meets the limitations of Claims 4 and 31. The "identifying, screening, characterising or designing a chemical entity which mimics or binds to FIH" is a preamble reciting an intended use, which does not contribute any structural limitations to the claimed method steps. The Hewitson et al. reference recites zinc(II) inhibits FIH (see middle of right column, page 26353) and in view of the assay using GST-HIF-1α-(775-826) as a substrate (see FIH Assays in bottom left column, page 26352), wherein the FIH of Hewitson et al. hydroxylate Asn803 of HIF (see title and bottom right column, page 26351); thus, the zinc meets the limitations of Claims 5-6 and 32-33. Thus, the method of Hewitson et al. anticipates Claims 1, 4-6, 29, 31-33.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 3 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hewitson et al. (May 31, 2002, The Journal of Biological Chemistry, vol. 149, page 26351-26355) in view of *In re Gulack* 217 USPQ 401 (Fed. Cir. 1983) and *In re Ngai* 70 USPQ2d 1862 (Fed. Cir. 2004). See MPEP §§ 2144 and 2144.04 regarding legal precedent as a source of rationale for rejection under 35 U.S.C. § 103.

Hewitson et al. teach as disclosed above.

Hewitson does not teach the use of the structural coordinate data of Table 3 as recited in the instant claims. However, this particular data required by the instant claims is considered to be nonfunctional descriptive material. In *Gulack* and *Ngai*, the respective Courts held that nonfunctional descriptive material cannot render nonobvious an invention that would have otherwise been obvious. According to *Gulack,* the key factor in analyzing the obviousness of the claims over the prior art is the determination that the machine-readable data comprising the structural coordinates of Table 3 is a known machine-readable medium and is unmodified. If the difference between the prior art and the claimed invention as a whole is limited to descriptive material stored on or employed by a machine, it is necessary to determine whether the descriptive material is functional descriptive material or nonfunctional descriptive material. According to MPEP 2106.01, functional descriptive material consists of data structures and computer programs which impart functionality when employed as a computer component. (The definition of data structure is a physical or logical relationship among data elements, designed to support specific data manipulation functions and that "Nonfunctional descriptive material" includes but is not limited to music, literary works, and a

compilation or mere arrangement of data. In this case, the data of Table 3 is an arrangement of data that represents a 3-D molecular structure. The data of Table 3 is not a data structure or a computer program that imparts functionality when employed as a computer component. The Appendix 3 structural coordinates are regarded as non-functional descriptive material and the claimed method is the same as the method of Hewitson et al. The data of Table 3, which are processed using a series of processing steps using a known algorithm, do not appear to impose a change in the processing steps or functioning of the computer and there is no evidence of record that the data of Table 3 imposes a change in the function of the computer. Put another way, the function of the computer is the same whether the computer comprises the data of Table 3 or not. Thus, all claim limitations concerning the structure coordinate data of Table 3 are given no patentable weight as the data is considered to be non-functional descriptive material.

Therefore, it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to employ the method as disclosed by Hewitson using any set of structural coordinates as defined in the claims with a reasonable expectation of success in view of the teachings of Hewitson et al. One would have been motivated to do this because Hewitson discloses the biological and structural implication "provide s a further target for the development of therapeutic agents that augment HIF activity in ischemia/hypoxic disease" (see bottom of left column, page 26354). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander D. Kim whose telephone number is (571) 272-5266. The examiner can normally be reached on 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Alexander Kim
July 24, 2007

RICHARD HUTSON, PH.D.
PRIMARY EXAMINER

Notice to Comply	Application No. 10/531,662	Applicant(s) Ratcliffe et al.	
	Examiner Alexander Kim	Art Unit 1656	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: See next page.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
For CRF Submission Help, call (703) 308-4212 or 308-2923
PatentIn Software Program Support
Technical Assistance.....703-287-0200
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PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY

7. cont.

The Table 2 contains many polypeptide without appropriate SEQ ID NOs. Appropriate correction is required.

The structural coordinates in Table 3 (total of four coordinates) teach an amino acid sequence since a particular atom is assigned to a linear amino acid sequence in order. As such, the amino acid sequence disclosed within the atomic coordinates must comply with the sequence rules. Labeling using a SEQ ID NO. must be inserted into the brief description of the drawings or into the Figure directly.

The polypeptide in page 35, line 16, does not have appropriate SEQ ID NO. Appropriate correction is required.

The polypeptide in Figure 3 or 4, require appropriate SEQ ID NOs. Appropriate correction is required.